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08/397,225	03/28/95	PERRICAUDET	M EX9301SG1-US

EXAMINER	
MILNE, A	

ART UNIT	PAPER NUMBER
1804	11

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DATE MAILED: 07/22/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 5-8-96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-3, 6 and 9-35 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 4-5, 7-8 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 6 and 9-35 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Claims 1-3, 6 and 9-35 are currently pending in U.S. Patent Application Number 08/397,225. The amendment filed 5-8-96 (paper #10) has been entered and carefully reviewed. Claims 4, 5, 7 and 8 have been cancelled as requested in the amendment filed 5-8-96.

The rejections based upon 35 U.S.C. 103 are hereby considered withdrawn in light of the amendment filed 5-8-96 (paper #10).

The rejections based upon 35 U.S.C. 112, second paragraph are hereby considered withdrawn in light of the amendment filed 5-8-96 (paper #10).

Claims 1-3, 6 and 9-35 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The specification has clearly succeeded in providing a utility for the claimed invention in terms of its use as a gene transfer vector. The credibility of the claimed invention is not part of the rejection of record. Credibility is a rejection under 35 U.S.C. 101. Further, the guidelines as published, Federal Register (60 FR 36263, July 14, 1995), clearly state that a rejection under 35 U.S.C. 112 "how to use" is entirely proper absent a rejection under 35 U.S.C. 101. The rejection of record is under 35 U.S.C. 112, "how to use". While the artisan may

consider the invention credible, this is not the same as having an enabling disclosure at the time of filing (i.e. 7/13/93). A utility for the claimed invention can be considered credible, and thus 101 is satisifed, while the specification does not teach how to use the claimed invention. The basic argument reiterated here, is that the specification does not provide sufficient guidance to the artisan regarding how to use the disclosed second generation adenoviral vectors for the purposes of delivering a therapeutic gene to any and all mammals.

The specification clearly discloses how to make the disclosed vectors that are to be used in gene transfer yet, simultaneously, the specification has not provided sufficient guidance to the skilled artisan regarding how to use the adenoviral vectors for the purposes as disclosed in the specification. The specification does not provide any correlatable *in vivo* results that one of skill in the art would be able to follow in attempting to reapeat the use of the disclosed adenoviral vectors. For example, page 2 of the specification provides the following:

> "The present invention indeed describes recombinant adenoviruses for gene therapy, which are capable of efficiently transferring DNA (up to 30 kb) *in vivo*, of expressing at high levels and in a stable manner this DNA in vivo, while limiting any risk of production of viral proteins, of transmission of the virus, of pathogenicity and the like."

It is respectfully pointed out to Applicants' that nowhere in the disclosed examples are any of these properties disclosed in a predictable fashion *in vitro* or *in vivo* such that the skilled artisan would know how to use the claimed vectors for the purposes as disclosed in the specification.

The specification does not disclose the proper modes of administration of the adenoviral vectors. For example, if said vectors are to be used in cancer therapy, then would it be critical to have them applied directly to a neoplasm, or would they be able to survive and express an exogenous DNA sequence at a level considered therapeutic by those of skill in the art, for a sufficient period of time to treat a pathology should they be injected i.v.?

More specifically, the specification discloses on pages 12 and 13 that the disclosed vectors are to be adminstered in the form of doses broadly ranging between 10^4 and 10^{14} pfu/ml and preferably 10^6 to 10^{10} pfu/ml. The specification does not provide enabling support for any of these concentrations aside from stipulating what possible therapeutic concentrations may be.

Even assuming that an effective combination of promoter and coding sequences exists, it is not clear that enough cells can be transfected to provide any therapeutic benefit. Several recent reviews indicate that efficient delivery and expression of foreign DNA has not yet been predictable by any method. Marshall states that "there has been no unambiguous evidence that genetic

treatment has produced therapeutic benefits" (p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col. 3). James Wilson, one skilled in the art, saying that " '{t}he actual vectors - how we're going to practice our trade - haven't been discovered yet" (p. 1055, col. 2). Culver et al. , reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge" (p. 178). Hodgson discusses the drawbacks of viral transduction and chemical transfection methods, and states that " {d}eveloping the techniques used in animal models, for therapeutic use in somatic cells, has not been straightforward" (pp. 459-460). Miller et al. also review the types of vectors available for *in vivo* gene therapy, and conclude that " for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances... targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col.1). Therefore even if the claimed second generation adenoviral vectors could provide a therapeutic effect

in vivo, it would require further experimentation to develop a suitable system for delivery of the gene construct.

It is well understood by the Examiner that the level of skill of the inventors of this invention is very high, especially in light of the vast amount of exciting publications produced by said inventors; however, it is concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 308-4213. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-4312.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Andrew Milne

7-11-96

Jasemine C. Chambers

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